## REMARKS

### I. General Remarks

Claims 8-16 have been canceled without prejudice or disclaimer. Claims 4-7 and 17-19 have been amended. Claims 20-31 have been added. Support for these claims can be found throughout the specification and claims as originally filed; no new matter has been added.

Claim 20 (which depends from allowed claim 1) recites preferred compounds of the present application, support for which can be found, for example, at pages 9-11 of the application as filed. Claims 21-23 recite the diseases or disorders previously recited in claims 9, 11 and 13, respectively, and are also supported at page 19 of the application as-filed. Claims 24-31 are derived from claim 4 as originally filed, and are also supported, for example, at pages 23-26 of the application as-filed. Upon entry of this Response, claims 1-7, 17-31 will be pending and at issue.

Applicants acknowledge with appreciation the confirmation that claims 1-5 are patentable over the prior art, as stated on page 9 of the Office Action. Since claims 6-7 and 17-31 share a unity of invention with claims 1-5, they too are patentable over the prior art.

### II. Rejections Under 35 U.S.C. § 101

Claims 14-16 are rejected as being improper process claims. Solely to advance prosecution, claims 14-16 have been canceled. Accordingly, this rejection is rendered moot. Applicants respectfully request reconsideration and withdrawal of the rejection.

### III. Rejections of the Claims Under 35 U.S.C. § 112, first paragraph

*A. Rejection of Claims 8, 10, and 12– Prevention of Specific Diseases and Disorders Is Purportedly Not Enabled*

Claims 8, 10 and 12 stand rejected as not enabled. The Examiner contends that, while the specification provides enablement for treating specific diseases and disorders, it does not enable preventing any of those diseases or disorders. Claims 8, 10 and 12 have been canceled, although the diseases and disorders recited therein are now recited in claims 21-23. While Applicants respectfully disagree with the Examiner's position, solely to advance prosecution, claims 21-23 do not recite a method of preventing the respective diseases or disorders.

Accordingly, this rejection has been rendered moot. Applicants respectfully request withdrawal of the rejection.

*B. Rejection of Claim 8-13 and 17-19 -- Treatment of Urological Disorders, Pain, and Inflammatory Disorders Is Purportedly Not Enabled*

Claims 8-13 and 17-19 stand rejected as not enabled. The Examiner contends that the specification does not enable use of the instant compounds of formula (I) to treat a urological disorder or disease, pain, or an inflammatory disease or disorder. Applicants respectfully disagree with the Examiner and request reconsideration in view of the Remarks below.

*I. Claims Drawn to Treating Pain and Urological Disorders Are Enabled*

a. VR1 Antagonists Result in Reduction of VR1 Activity

The specification provides data in Example 1-1, Example 1-2 and Table 1 (see pages 50-58 of the specification) analyzed under the protocol set forth in Assay 1. That data demonstrates the VR1 antagonist behavior of the presently claimed compounds. More specifically, the capsaicin-induced $Ca^{2+}$ influx in a human VR1-transfected cell line was measured in the presence of each of the 25 compounds synthesized in Examples 1-1 to 1-25. (See pages 31-32 of the specification for additional details regarding the assay.) The compounds are grouped in four classes based on activity: $IC_{50}$ = A ($\leq$ 0.1 μM) < B ($\leq$ 0.5 μM) < C ($\leq$ 1 μM) <D. Table 1 shows that each of the 25 compounds in Examples 1-1 to 1-25 has an activity falling within Class A -- the highest class listed -- which confirms that these compounds cause a strong reduction in VR1 activity and, hence are VR1 antagonists.

b. Correlation Between VR1 Activity and Pain and Urological Disorders

In the arena of pain management, it is known that both VR1 agonists (e.g. capsaicin) and VR1 antagonists can reduce VR1 activity, which, in turn, is correlated to a reduction in the perception of pain. (See, *e.g.*, J. Biol. Chem., Vol. 280, Issue 14, 13424-13432, April 8, 2005; Cheminform, Vol. 35, Issue 12 (2004), attached as Exhibits A-B.) VR1 agonists can cause a reduction in VR1 activity via an initial activation and subsequent de-sensitizing step that follows initial activation of VR1 activity. In contrast, VR1 antagonists reduce VR1 activity without inducing any initial stimulatory response.

Just as with pain management, reducing VR1 activity is known to be useful in the treatment of urological disorders. In subjects with overactive bladders or spinal cord injuries, or confronted with other situations in which noxious stimuli are involved, C-fibers become active and convey a signal to the spinal cord resulting in a feeling of urgency to urinate or an increase in the frequency of urination. By ultimately desentisitizing VR1 activity, agonists, such as capsaicin have been shown to have therapeutic utility in treating such conditions. (See C.J. Fowler et al., Lancet (1992) 339 1239, attached as Exhibit C.)

It has also been shown that VR1 antagonists, such as capsazepine can displace the binding of radiolabelled resiniferatoxin (a naturally occurring VR1 agonist, used clinically for treating overactive bladder) in bladder membranes. (See A. Szallasi et al., J. Pharmacol Exp. Therapeutics, (1993) 267, 728-733, attached as Exhibit D.) Thus, it was known that VR1 antagonists have a similar effect as VR1 agonists on bladder membranes.

Almost immediately thereafter it was also shown that capsazepine had a functional effect on the isolated rat bladder *ex vivo* -- as demonstrated by its inhibition of the contractile responses to capsaicin. (See C.A. Maggi et al., British Journal of Pharmacology (1993) 108, 801-805, attached as Exhibit E). This demonstration set the foundation for the development of further VR1 antagonists to treat urological disorders. (See P. Whal, C. Foged, S. Tullinn, C. Thomsen, Molecular Pharmacology (2001) 59, 9-15; Y. Wang et al., Molecular Pharmacology (2002) 62, 947-956, attached as Exhibit F.)

*c.* Correlation Between VR1 Activity and Inflammatory Disorders

As noted above, VR1 agonists cause an eventual reduction in VR1 activity through a de-sensitizing step that follows an initial activation step. During the initial activation step, capsaicin leads to the release of neurotransmitters from both peripheral and central nerve endings, causing a set of inflammatory responses (often referred to as neurogenic inflammation), which, in turn, result in bronchoconstriction, plasma extravasation and mucus hypersecretion. (See H. Kanazawa et al., Eur Respir J, (1998) 12, 1307-1312, attached as Exhibit G (bronchoconstriction); M.G. Belvisi, Curr Opin Pharmacol (2003) 3, 239-243, attached as Exhibit H (plasma extravazation); and M.G. Belvisi, Pulm Pharamcol Ther (2003) 16, 1-7, attached as Exhibit I (mucus secretion).)

VR1 antagonists have been shown to reduce the capsaicin-induced cough response. For example, capsazepine has been found to inhibit the cough response induced by

capsaicin and citric acid. (See, M.G. Belvisi et al., P.J. Barnes, Eur J Pharmacol (1992) 215, 341-344, attached as Exhibit J; and U.G. Lalloo et al., J Appl Physiol (1995) 79, 1082-1087, attached as Exhibit K.) Similarly, iodo-resiniferatoxin (a potent VR1 antagonist) has also shown to inhibit capsaicin-induced cough in animals. (See M. Trevisani et al., Thorax (2004) 59, 769-772, attached as Exhibit L.)

Given a) the demonstration in the specification that the claimed compounds function as VR1 antagonists; and b) the known correlation between VR1 antagonism and treating pain, and urological and inflammatory disorders, Applicants respectfully submit that the presently claimed compounds are enabled for the treatment of pain and urological disorders.

## IV. Rejections of the Claims Under 35 U.S.C. § 112, second paragraph

Claims 6-19 stand rejected as indefinite. In particular, the Examiner contends that claims 6-10 and 12 lack antecedent basis and that claims 11 and 13 are unclear. Applicants thank the Examiner for the attention to this detail. Claims 6 and 7 have been amended to depend from claim 5, and claims 8-13 have been canceled without prejudice.

In addition, the Examiner contends that claims 14-16 do not set forth any steps involved in the methods/processes claimed. Solely to advance prosecution, claims 14-16 have been canceled.

Lastly, the Examiner contends that claims 17-19 are unclear according to standard U.S. patent practice. Claims 17-19 have been amended to bring them in line with customary practice. Applicants respectfully request reconsideration and withdrawal of the rejection.

## V. No Waiver

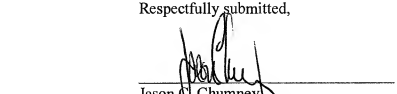
All of Applicants' arguments and amendments are without prejudice or disclaimer. Additionally, Applicants have provided some arguments that undermine the positions taken by the Examiner and, in turn, support the patentability of the claims. Other arguments may exist, and Applicants reserve the right to rely on the same at a later point, if appropriate. To the extent Applicants have not responded to all statements made by the Examiner, their silence should not be construed as any form of acquiescence or preclude them from addressing the same at a later point, if appropriate. The arguments raised by Applicants are sufficient to overcome the Examiner's rejections.

## SUMMARY

In light of the above remarks, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections. Applicants further submit that the application is now in condition for allowance, and they earnestly solicit timely notice of the same. Should the Examiner have any questions, comments or suggestions in furtherance of the prosecution of this application, the Examiner is invited to contact the attorney of record.

Applicants believe that there are no fees due in association with the filing of this Response, apart from the fee for extension of time. However, should the Commissioner deem that any additional fees are due, including any fees for extensions of time, the Commissioner is authorized to debit Baker Botts L.L.P. Deposit Account No. 02-0383, Order Number 078503.0105, for any underpayment of fees that may be due in association with this filing.

Respectfully submitted,



Jason C. Chumney
Patent Registration No. 54,781

Attorney for Applicant
Telephone: 212-408-2500

Baker Botts L.L.P.
30 Rockefeller Center
New York, NY 10112

Date: February 17, 2009